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# Executive Attention in Schizophrenic Males and the Impact of COMT Val$^{108/158}$Met Genotype on Performance on the Attention Network Test

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***Background*: Executive control of attention in schizophrenia has recently been assessed by means of the Attention Network Test (ANT). In the past, for tasks assessing executive attention, findings in schizophrenia have been contradictory, among others suggesting a lack of increased stimulus interference effects. Attention and executive functioning are substantially influenced by candidate genes of schizophrenia, including the functional single-nucleotide polymorphism catechol-*o*-methyltransferase (COMT) Val$^{108/158}$Met, with task-dependent, specific effects of Met allele load on cognitive function. Therefore, we aimed at investigating executive attention in schizophrenic patients (SZP) as compared with healthy controls (HC), and to assess the specific impact of COMT Val$^{108/158}$ Met on executive attention, using ANT. *Methods*: We applied ANT to 63 SZP and 40 HC. We calculated a general linear model to investigate the influence of affection status and the COMT Val$^{108/158}$Met genotype on executive attention as assessed by the ANT. *Results*: Multivariate analysis of variance revealed a significant effect of group on executive attention. SZP exhibited smaller conflict effects in the ANT. Met allele load significantly modulated executive attention efficiency, with homozygous Met individuals showing low overall reaction time but increased effects conflicting stimulus information in executive attention. *Conclusions*: Our data suggest a disease-related dissociation of executive attention with reduced conflict effects in SZP. Furthermore, they support the hypothesis of differential tonic-phasic dopamine activation and specific dopamine level effects in different cognitive tasks, which helps interpreting contradictory findings of Met allele load on cognitive performance. Disease status seems to modulate the impact of COMT Val$^{108/158}$Met on cognitive performance.**

*Key words:* schizophrenia/endophenotype/genetics/attention/dopamine

## Introduction

Deficits in cognitive domains, eg, executive performance,[1] working memory,[2] and sustained attention,[3,4] are considered core features of schizophrenia and represent attractive candidate endophenotypes for investigations on the genetic background of the disease.[5] However, results on executive control of attention and effects of incongruent stimulus information in schizophrenia have been contradictory.[6] Several authors reported relatively preserved cognitive control of attention and a lack of increased stimulus interference effects in patients with the disease.[7,8] However, studies applied different tasks for assessment of executive control of attention, which might derogate direct comparability of findings.

The Attention Network Test (ANT) examines executive control of attention, alerting, and orienting as distinct and independently measurable components of the cortical and subcortical attention network,[9] the subcortical network component being reflected by alerting and orienting measures in the test. The conflict condition of the ANT results in robust effects in terms of reaction time (RT) delays in healthy subjects[10] and reliably assesses efficiency of conflict processing. Functional magnetic resonance imaging studies have demonstrated activation of the dorsal anterior cingulate cortex (dACC) during conflict conditions, confirming the involvement of the dACC in conflict processing and executive control.[11] Recently, our group used visual event-related potentials to localize neural generators of conflict processing during ANT.[12] Schizophrenic patients (SZP) lacked modulation of P300 amplitude and latency and displayed deficient dACC activation during conflict processing, consistent with previous reports about dysfunctional dACC activation in schizophrenia.[13] Furthermore, patients displayed

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significantly reduced conflict effects as compared with healthy controls.

The eligibility of the use of ANT as a tool to identify potential endophenotypes is supported by reports demonstrating that efficiency of conflict processing as measured by the ANT is heritable.[14] Regarding effects of single-nucleotide polymorphisms (SNPs) on conflict processing in ANT, SNPs resulting in increased cortical dopamine levels (eg, genes encoding catechol-*o*-methyltransferase [COMT], monoamine oxidase A, and dopamine receptor 4) were reported to result in decreased executive attention and conflict processing efficiency, as reflected by larger conflict effect scores.[15] Although higher cortical dopamine levels have generally been considered advantageous for executive performance, the finding is consistent with the more differentiated view that genetic variants resulting in enhanced levels of cortical dopamine might exert disadvantageous effects in tasks involving conflict processing,[16] demanding phasic $D_2$-mediated activation rather than stable tonic $D_1$-mediated activation.[17]

The intensively investigated functional COMT $Val^{108/158}$ Met polymorphism (rs4860), a G>A transition, exerts its effects primarily by determination of dopamine catabolism in the prefrontal cortex (PFC), thereby critically influencing dopamine-dependent prefrontal functioning.[18] A 3-fold decrease of enzymatic activity of the membrane-bound allozyme MB-COMT was found in the brain tissue of homozygous $COMT^{Met/Met}$ individuals.[19] As reviewed recently,[20] current research efforts have established the relationship of an inverted U–shape function between dopamine and PFC function, determined not only by genetic variation in the COMT gene itself but also depending on the individual's genetic and environmental background. Because dopamine level manipulation in both directions can exert beneficial and detrimental effects,[21,22] it has been suggested that the specific task which is investigated might be a crucial determinant of the polymorphism's impact on performance. The 'tonic-phasic dopamine hypothesis' states that Met allele is associated with (a) subcortically decreased phasic and increased tonic dopamine transmission and (b) cortically increased dopamine concentration. Against this background, the Met allele enhances stability by increased $D_1$-related dopamine transmission but lowers performance in tasks involving cognitive flexibility and conflict processing, which requires phasic, $D_2$-related cortical activation.[23] In contrast, the Val allele results in (a) subcortically increased phasic, decreased tonic dopamine transmission and (b) cortically decreased dopamine concentration, thereby enhancing $D_2$-related transmission and facilitating switching to alternate network activation states and flexibility in behavioral programs.[24] However, several studies investigating the impact of $Val^{108/158}$Met on cognitive phenotypes have not yielded conclusive results, mainly due to the complexity of involved cognitive processes. It has therefore been suggested to employ more specific tasks that lack activation of additional neurotransmitter systems. More specifically, attentional set maintenance and response inhibition in conflict paradigms have been recommended as promising tasks in studies aiming at elucidating phenotypic associations with $Val^{108/158}$Met.[24]

Therefore, the aim of this study is to investigate the efficiency of executive attention in SZP as compared with healthy individuals and the impact of the COMT $Val^{108/158}$Met genotype on executive control of attention in a test involving a simple, distinctively measurable attentional conflict paradigm. We applied the ANT, which provides distinct assessment of executive attention in terms of response inhibition and conflict processing. We hypothesized that (a) carriers of the Met allele would show increased effects of stimulus incongruency in conflict processing and that (b) SZP would display smaller conflict effects than healthy individuals, based on lowered dopamine levels that are modulated by the complex, disease-conferring genetic background including COMT.

## Materials and Methods

### *Participants*

Participants were 63 schizophrenic subjects (22 female, 41 male) in inpatient and outpatient care and 40 HC (13 female, 27 male) without history of substance abuse or family history of psychiatric or neurological disorders. Mental health status of controls was assessed by trained psychiatrists by means of the Mini International Neuropsychiatric Interview.[25] All participants self-reported Caucasian descent. Patients were recruited at the Department of Psychiatry and Psychotherapy, Campus Benjamin Franklin, Charité—University Medicine Berlin, and were diagnosed with schizophrenia according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria (American Psychiatric Association, 1994) by trained psychiatrists. We included patients recovering from acute illness episodes as well as chronic but stable patients. Sufficient clinical stability was assessed using the Positive and Negative Syndrome Scale (PANSS),[26] with patients exceeding a PANSS total score of 75, corresponding to "moderately ill"[27] being excluded from participation. All patients, except 2 patients who underwent monotherapy with flupentixol decanoate, received a treatment regimen with second-generation antipsychotics (SGAs); 12 patients received 2 second-generation agents. History of severe head injury with loss of consciousness, current substance abuse, or estimated premorbid IQ below 85 (according to standardized IQ assessment, see "Cognitive Testing") led to exclusion from participation. The German test Mehrfachwortschatztest[28] was employed to quantify premorbid verbal intelligence.

Testing was administered after written fully informed consent was obtained. The study was approved by the ethics committee of the Charité Berlin and was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

### *Cognitive Testing*

Test conditions followed standard procedures of neurocognitive testing. The experimental task and design of ANT followed the original program[10] and is described in detail elsewhere.[12] Briefly, pressing either a left or a right button indicated the direction of a central target arrow, irrespective of flanking conditions. Flankers were lines (neutral target condition) or arrows pointing to the same (congruent target condition) or opposite direction (incongruent target condition). Cues were present or absent and were displayed as double, center, or spatial cues. A total of 288 trials were performed. Subjects were instructed to respond as fast and as accurately as possible. Attention network effects were calculated based on RT differences during different conditions (alerting = RT targets [no cue] − RT targets [double cue]; orienting = RT targets [center cue] − RT targets [spatial cue]; conflict = RT incongruent targets − RT congruent targets. Ratios were calculated (conflict effect [milliseconds]/mean RT [milliseconds]) to take into account the potentially confounding effect of overall mean RT.

### *SNP Genotyping*

Genotyping of the SNP rs4680 (COMT c.675 G>A, p.Val158Met) was carried out at the Gene Mapping Center of the Max Delbrück Center in Berlin. Genotypes of rs4680 were determined by a TaqMan 5′-exonuclease assay, as described previously.[29] The call rate in more than 2500 individuals, including the present samples, was >99%. The genotyping reliability of the TaqMan assay was examined by genotyping of 186 duplicated DNA samples that are not part of the present study. All duplicated samples displayed the same genotype as its reference sample. Mendelian inheritance was demonstrated in 80 nuclear families. Potential DNA admixture of study samples was excluded by genotyping of 20 highly polymorphic microsatellite markers.

### *Statistical Analysis*

Significant demographic differences between groups were assessed using 1-way analysis of variance (ANOVA) and Pearson chi-square ($\chi^2$) test. Because the effect of COMT Val$^{108/158}$Met genotype is regarded additive, we computed association with disease applying the allele-based Cochran-Armitage trend test. However, genotype distribution was also analyzed by means of a $\chi^2$ test (2 *df*). Association with disease, though, was not the focus of the study, which would be highly underpowered for this approach. We performed multivariate analysis of variance (MANOVA) to assess differences in the executive attentional network between groups and genotypes. Based on our own (C. Urbanek, A. H. Neuhaus, C. Opgen-Rhein, S. Strathmann, N. Wieseke, P. Schlattmann, R.T. Schaub, M. Dettling, unpublished data) and others' previous negative findings[30] regarding the orienting and alerting networks and to address the problem of multiple testing, we restricted analyses to the executive attentional network. Main effects for genotype, group, and their interaction were computed. Sex and years of education were included in the analysis as cofactor and covariate, respectively. Contrasts were computed for group, sex, and genotype. Because age did not show statistically significant difference between groups, this potential covariate was not included in the MANOVA. All analyses were performed using the Statistical Package for the Social Sciences, Version 13.0 for Windows (SPSS GmbH Software, Munich, Germany). All tests were performed with a 2-sided $P < .05$.

**Table 1.** Demographic and Clinic Characteristics of Schizophrenic Patients (SZP) and Healthy Controls (HC)

| | SZP, $N = 63$, Mean (SD) | HC, $N = 40$, Mean (SD) | $F$ (*df*) | $P$ |
|---|---|---|---|---|
| Age, y | 37.5 (±10.4) | 34.6 (±9.8) | 1.96 (1) | .165 |
| Education, y | 12.7 (±2.5) | 14.3 (±2.3) | 9.76 (1) | .002 |
| Sex, % male | 56.1 | 67.5 | (1) | .834[a] |
| MWT-IQ | 104.3 (±14.9) | 114.4 (±16.6) | 10.27 (1) | .002 |
| DOI, mo | 77.8 (±90.5) | — | — | — |
| PANSS pos | 14.1 (±5.8) | — | — | — |
| PANSS neg | 18.1 (±7.3) | — | — | — |
| PANSS gen | 32.1 (±13.7) | — | — | — |

*Note*: MWT-IQ, premorbid verbal IQ as measured by the Mehrfachwortschatztest (German); DOI, duration of illness; PANSS, Positive and Negative Syndrome Scale; PANSS pos, PANSS positive symptom subscale; PANSS neg, PANSS negative symptom subscale; PANSS gen, PANSS general symptom subscale.
[a]Significance as calculated by Pearson chi-square (1 *df*) for sex distribution.

## Results

One-way ANOVA revealed significant differences between SZP and HC with regard to premorbid verbal intelligence scores and years of education but not age (table 1). Sex distribution did not differ between groups as assessed by Pearson $\chi^2$ test.

The Val$^{108/158}$Met allele frequencies did not show deviations from Hardy-Weinberg equilibrium in either group (Pearson $\chi^2$, $P = .599$ and $P = .461$, respectively). As assessed by the allele-based Cochran-Armitage trend test, the Met allele showed a significantly higher frequency in the patient group, as shown in table 2.

Mean RT (644.8, ±130.3) was significantly higher in SZP than in HC (561.3, ±84.6, $P < .001$) as assessed by

**Table 2.** Genotype and Allele Frequencies for COMT Val$^{158/108}$Met in SZP and HC

| Group | Val/Val | Val/Met | Met/Met | $P^a$ | Val | Met | $P^b$ |
|---|---|---|---|---|---|---|---|
| SZP (%) | 11 (17.5) | 34 (54) | 18 (28.5) | **.012** | 56 (44.4) | 70 (55.6) | **.038** |
| HC (%) | 13 (32.5) | 21 (52.5) | 6 (15) | | 47 (58.7) | 33 (41.3) | |

*Note*: COMT, catechol-*o*-methyltransferase; SZP, schizophrenic patients; HC, healthy controls.
[a]Differences of genotype frequencies in SZP and HC, by Pearson chi-square (2 *df*).
[b]Allele-based Cochran-Armitage trend test.

Mann-Whitney test for 2 independent samples (figure 1). Conflict effect scores were smaller in the schizophrenic group (92.1, ±49.5) as compared with HC (106.1, ±59.9, figure 2). Interestingly, schizophrenic males exhibited the smallest conflict effect (81.4, ±37.1). MANOVA revealed a main effect for group ($P < .001$), genotype ($P = .011$), and sex ($P = .040$) but not for education years ($P = .132$). The interaction of group by genotype was significant ($P = .046$). This was not the case for the interaction of sex and genotype ($P = .391$). The main effect of group was reflected by a statistically significant effect of group on both conflict effect and ratio scores in ANOVAs (table 3). Years of education showed an influence on the conflict effect scores at trend level ($P = .054$) and significant influence on conflict effect ratio ($P = .044$). Contrast analyses revealed significantly lower conflict effects in SZP than in controls ($P = .015$). Furthermore, in ANOVAs, sex influenced the conflict effect on a trend level ($P = .077$). Interestingly, in contrasts, female individuals demonstrated a trend to higher conflict effects (111.3 ± 53.7) as compared with male individuals (90.4 ± 53.0; $P = .07$). The group by sex by genotype, but not group by sex interaction yielded trend values ($P = .08$). For more detailed information on RTs and conflict effects of each group, see Supplementary Material.

As depicted in figure 3, COMT Val$^{108/158}$Met genotype displayed a significant influence on conflict effect scores, with COMT$^{Met/Met}$ homozygous subjects exhibiting higher scores than COMT$^{Val/Val}$ homozygous or heterozygous COMT$^{Val/Met}$ subjects, as revealed in contrast analyses (table 3). The genotype effect on conflict processing was especially true for healthy males and females but seemed to be less prominent in schizophrenic females and to be diminished in schizophrenic males, as depicted in figure 4. However, the sex by genotype or sex by genotype by group interaction was not significant. Group by genotype interaction showed trend values ($P = .08$).

In patients but not controls, the conflict effect was positively correlated with mean RT (Pearson correlation = .393, $P = .001$, and .213, $P = .193$, respectively). Separate correlation analysis for schizophrenic females and males revealed that the observed correlation was mainly based on the positive correlation in the latter

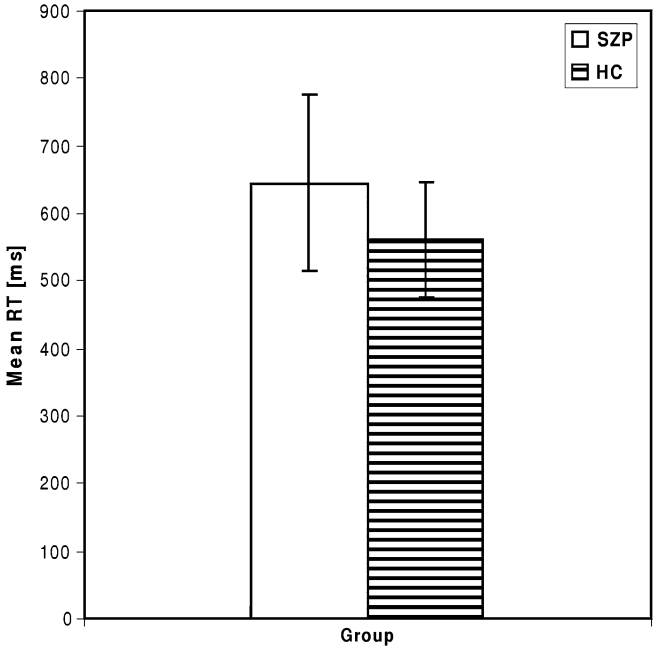


**Fig. 1.** Mean Reaction Time (RT, ±SD) in Schizophrenic Patients (SZP) and Healthy Controls (HC).

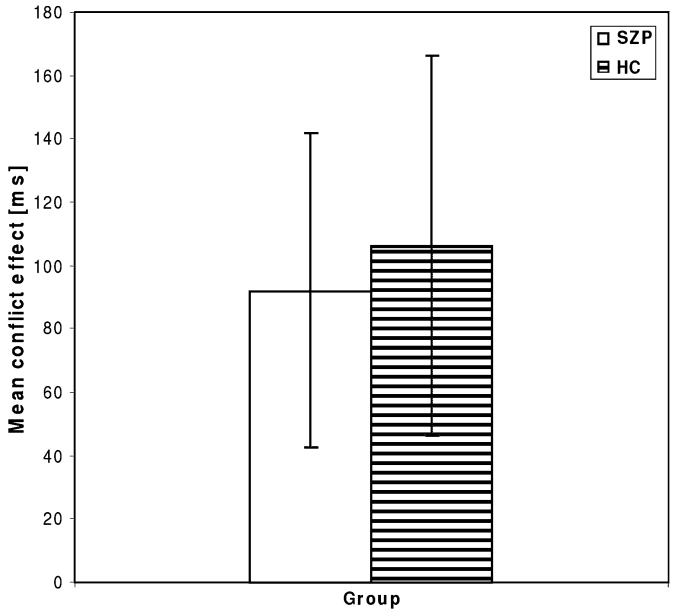


**Fig. 2.** Mean Conflict Effect Scores (±SD) in Schizophrenic Patients (SZP) and Healthy Controls (HC).

**Table 3.** Impact of catechol-*o*-methyltransferase (COMT) Val$^{108/158}$ Met Genotype and Group on Conflict Effect Scores (Analyses of Variance), with Main Effects of Genotype, Group, and Their Interaction

| | Main Effect | | | | | |
|---|---|---|---|---|---|---|
| | Group | | Genotype | | Group x Genotype | |
| | *F* (*df*) | *P* | *F* (*df*) | *P* | *F* (*df*) | *P* |
| Conflict effect | 6.1 (1) | .015 | 3.7 (2) | .028[a] | 1.8 (2) | .166 |

[a]Contrasts revealed significantly higher conflict scores in COMT$^{Met/Met}$ than in COMT$^{Val/Met}$ ($P$ = **.031**) and in COMT$^{Val/Val}$ subjects ($P$ = **.008**).

subgroup (Pearson correlation = .319, $P$ = .148, and .341, $P$ = .029, respectively). Conflict effect scores were not correlated with total error rate in conflict conditions or with omission rate in patients (Pearson correlation −.066, $P$ = .607 and −.100, $P$ = .435, respectively) or in controls (Pearson correlation .220, $P$ = .179 and −.146, $P$ = .374, respectively).

## Discussion

The aim of the study was to investigate executive control of attention in SZP by means of the recently developed ANT. Conflict and stimulus interference processing in schizophrenia have been subject to discussion[7] due to reports on relatively preserved cognitive control of attention in the disease. Based on these and on our own findings in a previous study,[12] we hypothesized that conflicting stimulus information might exert less detrimental effects on stimulus processing in SZP than in controls.

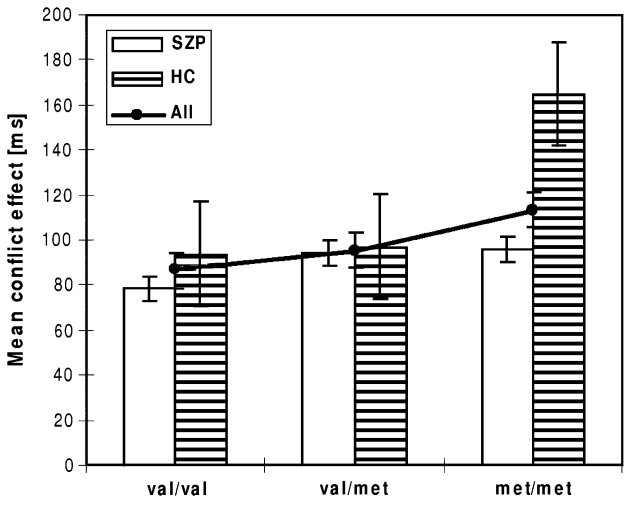


**Fig. 3.** Catechol-*o*-methyltransferase Val$^{108/158}$ Met Genotype Impact on Conflict Effect Scores (±SE) in Schizophrenic Patients (SZP) and Healthy Controls (HC).

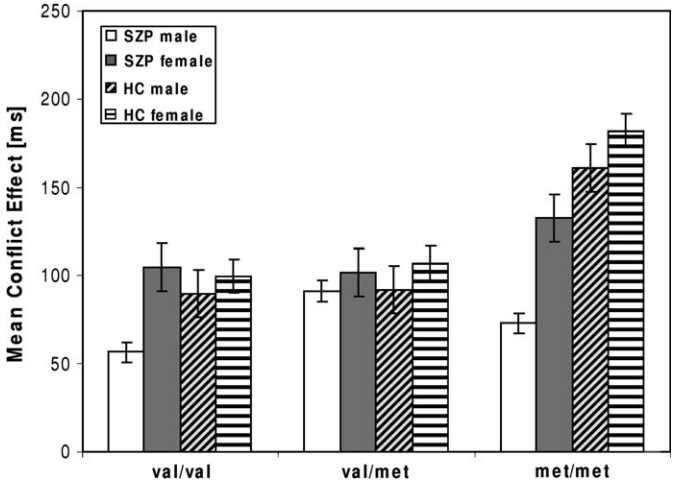


**Fig. 4.** Sex- and Group-Dependent Impact of catechol-*o*-methyltransferase Val$^{108/158}$ Met Genotype on Conflict Effect in Schizophrenic Patients (SZP) and Healthy Controls (HC). Conflict effect (±SE) for each group (means and SD for each are given in Table A of Supplementary Material).

Furthermore, we aimed at investigating the impact of COMT Val$^{108/158}$Met genotype, for which specific, task-related effects have been claimed, on conflict processing in the ANT. We hypothesized that the Met allele would be related to larger conflict effects.

The observed reduced conflict effect in SZP in our sample is contradictory to the very first report on ANT performance in SZP of Wang et al[30] who reported increased conflict effects. However, in the antecedent study, more female than male patients were included. Sex effects were not investigated. Interestingly, our finding is primarily due to the substantially diminished conflict effect in a subgroup of our patient sample, the schizophrenic males. The reduction of conflict effect (or "conflict cost") in these subjects cannot be explained by a simple speed accuracy trade-off, because conflict effect scores did not show correlation with error or omission rates in this population. However, there was a positive correlation between conflict effect scores and mean RT, ie, higher conflict effects were associated with higher mean RT. This was not true for HC or for schizophrenic females (who displayed high mean RT), which makes the explanation of decreased conflict effect as an artifact of general slowing of RT unlikely.

The observation that male SZP display reduced conflict effects as compared with HC might also seem contradictory to the numerous reports on impaired executive control and problem solving in SZP; however, our findings are consistent with findings of a recent study[31] that revealed reduced interference effects of incongruent flankers in SZP as compared with HC. Interestingly, solely males were investigated in this study. The finding is in line with several reports outlining the possibility that in fact conflict processing and stimulus incongruency monitoring is preserved in schizophrenia, reflected by

a lack of increased interference effects as compared with controls.[7,8] These findings could not be explained by increased error rates in subsequent studies.[32] Similarly, a recent study applying semantic stimuli demonstrated that patients are able to process incongruent stimulus information using cognitive control.[33] However, different paradigms and stimuli have been applied in these studies, thus leaving the exact nature of perceptional and attentional strategies in schizophrenia a subject to further clarification. With respect to conflict and stimulus incongruency processing in the ANT, however, a reduced depth of perceptional encoding of stimuli, independent of their distractor or target status,[34] was claimed to cause the reduced conflict cost in schizophrenia.[31]

In our sample, Met allele was more frequent in schizophrenia, which is in contrast to the majority of comparable studies.[35,36] However, other studies have also found increased Met load in schizophrenia.[37] Thus, our result may reflect the inconsistency of allelic association with schizophrenia across studies. Glatt et al[38] have suggested that case-control studies might be biased toward Met allele load in schizophrenia, potentially due to population stratification effects. Further, allele load *per se* might be of secondary interest for disease risk because the COMT gene seems to exert only minor influence on general susceptibility for schizophrenia. Rather, it contributes—in interaction with environmental factors and with further genetic variants—to the disease by determining a subject's dopamine state and related cognitive brain functions.[39] Regarding genotype effects on conflict processing, our findings are consistent with previous reports,[15] in which increased conflict effects for individuals homozygous for COMT$^{Met/Met}$ was reported. Interestingly, subjects referred to as "high dopamine level subjects," based on the subject being homozygous for the Met allele at the COMT Val$^{108/158}$Met locus and also being homozygous for the 4-repeat allele at the monoamine oxidase A-linked polymorphic region, exhibited highest conflict effects. This finding underlines the substantial impact of the complex genetic background on which COMT exerts its effects on executive performance. Furthermore, the association of high Met allele loading with impaired conflict monitoring in the ANT is consistent with previous findings in studies applying interference paradigms, when considering the "tonic-phasic dopamine hypothesis."[40] This hypothesis was applied to integrate conflicting results regarding the effects of dopamine level on cognitive performance; it states that a high dopamine level is associated with impaired conflict processing and cognitive flexibility.[41]

Generally, a high Met allele load has been associated with improved executive function,[42,43] attention,[23] and working memory.[44] However, in a study applying tasks that require alternation between response rules, the Met allele was associated with enhanced performance in imitation learning, but with impaired performance in reversal learning that demands behavioral inhibition and conflict processing.[16] Furthermore, association of high Met allele load with reduced RT variability in the Continuous Performance Test suggested that the Met allele confers enhanced stability in tasks demanding tonic, $D_1$-mediated dopamine activation, eg, attention and working memory maintenance, by stabilizing active neural representations but might exert negative effects on performance in tasks requiring phasic, $D_2$-mediated activation, essential for updating working memory traces and facilitating cognitive flexibility and conflict processing.[17] In children, however, the Met allele has been associated with better performance in a conflict-related task.[45] The dopamine status[46] and functioning of executive networks in children, though, is subject to large-scale developmental changes[47] and might therefore not be applicable to direct comparison with adult individuals.

Executive control of attention requires responses to one but not another aspect of a stimulus and is involved in self-regulation of cognition and emotions.[48,49] This is in line with reports that the Met allele is associated with disorders implying dysfunctional cognitive control of impulsive and aggressive behavior.[50,51] In contrast, Blasi et al[52] reported that the Met allele was associated with better performance in a new test for assessment of attentional control. However, in that study, the key variable was response accuracy, as opposed to RT in our study.

As outlined by Tunbridge et al[20] in their review on the inverted U–shape model of dopamine action,[53] and the role of COMT Val$^{108/158}$Met, the polymorphism determines a subject's dopamine state and related cognitive performance against the background of complex genetic and environmental interaction. In this model, the effect of COMT activity on PFC-related functions, eg, working memory, depends on multiple factors—including the amount of stress, other loci in the gene, and pharmacological intervention. Impairment of working memory after local infusion of both $D_1$-antagonists and -agonists has been related to complex interaction of $D_2$- and $D_1$-receptor activation.[54] The effects of antipsychotic medication have to be taken into account for interpretation of COMT Val$^{108/158}$Met effects on conflict processing in this population. All SGAs, while varying widely regarding receptor affinity, have the $D_2$-receptor blockade as a common mechanism of action; $D_1$-receptor affinity, however, is negligible.[55] It has been proposed that, in combination with antagonism at 5-hydroxytryptamine (serotonin) receptor 2a, SGAs induce a preferential dopamine release in the PFC.[56] Therefore, in theory, atypical antipsychotic medication could interact with genotype regarding prefrontal dopamine levels by "pushing the individual nearer to the peak" of the inverted U–shaped curve, ie, to increased prefrontal dopamine level, as has been demonstrated for amphetamines under controlled conditions.[21] In our patient sample, this would translate into enhanced prefrontal dopamine concentration and conflict effect, irrespective of their disease-related, potentially

dopamine-lowering, genetic background. However, when included into the general linear model as a covariate, medication (in chlorpromazine equivalents) did not exert effects on conflict effect scores ($P = .96$). This might be due to the diversity of specific receptor occupancy thresholds and of receptor affinity and availability over time, among the various substances.[55] Therefore, multiple confounding factors have to be taken into account, including other loci in the gene as well as environmental influences that might not have been controlled for in our study.

COMT remains an interesting and plausible candidate for the investigation of the genetic background of cognitive performance in schizophrenia because (a) the gene maps to 22q11.2, a chromosomal region that is linked to susceptibility for schizophrenia itself,[57,58] and is located in the critical deletion region of velo-cardio-facial syndrome which is highly associated with schizophreniform disorders[59]; (b) the variant is functional, altering dopamine disposability in the brain, disturbances of which are considered displaying one of the major pathomechanisms in schizophrenia[60,61]; and (c) efficient dopamine tonus in the PFC is crucial for cognitive functioning, deficits of which are considered core features of schizophrenia.[62] Particularly, executive attention and interference monitoring are modulated by dopamine[63] and have been mapped to a common network of brain regions including the dACC, the specific contribution of which has been demonstrated in functional imaging studies.[64]

The observed differences between males and females in our study with regard to executive attention were not the primary focus of our investigation, but have previously been observed by our group (Urbanek et al, submitted) and have also been reported in a study focusing on the genetic underpinnings of attentional networks.[15] In the latter study, applying the ANT to healthy individuals, conflict effect scores were highest for female COMT$^{Met/Met}$ individuals, suggesting a potential interaction of sex by genotype with regard to conflict processing. This view receives support by reports on sex-specific effects in COMT loss-of-function mouse models on behavior.[65] Because this variable did only yield trend values, however, as a main and interaction factor for conflict processing in our sample, the observation should be interpreted with caution. However, it recapitulates findings of sex-dependent impact of COMT in other phenotypes, eg, obsessive compulsive disorder,[66] and is supported by findings that the expression of the COMT gene is subject to several regulatory systems, including numerous estrogen response elements.[67]

Therefore, considering both the ''tonic-phasic dopamine hypothesis'' and the above mentioned view of an U-shaped relationship between dopamine level and cognitive functioning, it is conceivable that the pattern of COMT impact on conflict processing observed in our sample reflects the interaction of COMT genotype with 2 factors—first, interaction with affection status, which is presumably associated with further genetic variation in COMT or other genes resulting in lower prefrontal dopamine level, that leads to decreased conflict effect scores in the respective group and second, an interaction with sex. The latter is not supported by strong statistical evidence, but one may assume so based on the assumption that female sex results in lower expression of COMT. This assumption is supported by the observation that estradiol downregulates COMT expression in cell cultures,[68] potentially leading to higher dopamine levels and to increased conflict effects in the respective group. However, because sex-by-genotype and group-by-genotype interactions did only yield trend values in our sample and because cell counts for homozygous subjects were low in most of the respective classes (group by sex), the particular nature of a potential sex-related effect, or possible interaction between these factors, clearly needs further clarification and replication.

The ANT is an attractive endophenotype for schizophrenia because it provides easily applicable assessment of distinct, separately measurable components of attention, each of which is closely related to specific cortical and subcortical regions and neurotransmitter systems. However, the ANT has not been applied to relatives of SZP. Our findings, in combination with previous reports, suggest a disease-related pattern of attentional network functioning, with reduced conflict effect scores in male schizophrenic individuals.

Several limitations of the study have to be taken into account. First, we investigated a heterogeneous, nonmatched sample. Cell counts in the respective genotype by sex groups were too low for further specific sufficiently powerful statistical analyses. Second, data on other potentially interacting genotypes at other functional SNPs of the gene, eg, the COMT P2 promoter region and 3′ region SNPs, were not available in our sample. Third, although statistically significant main effects were detected, the power of our study might be low as a sample size of 600 subjects was suggested to efficiently investigate genotype effects on attentional networks.[15] Fourth, as discussed above, a possible, but probably rather weak effect of antipsychotic medication on performance in executive attention and conflict processing in our schizophrenic sample cannot entirely be ruled out.

However, the findings encourage further investigation of executive attention as a putative endophenotype of schizophrenia because they challenge the view of a general, unspecified impairment of executive and attentional performance in the disease. Additionally, previous findings of a potential role of sex regarding executive attentional control and regarding COMT Val$^{108/158}$Met genotype impact on this variable are supported. The suggestive sex differences in our sample underline the importance of a differentiated consideration of conflict processing because sex might potentially impact on results of attentional networks in psychiatric diseases.

## Supplementary Material

Supplementary tables are available online at http://schizophreniabulletin.oxfordjournals.org.

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